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Basal cell carcinoma: a paradigm for targeted therapies

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Abstract: INTRODUCTION: Basal cell carcinoma (BCC) is the most frequent cancer with increasing incidence over the last decades. Standard of care is surgical excision, upon which complete tumour clearance is achieved in most cases. However, a small subgroup of patients will have remnants of disease post-excision and require further treatment options. Over 90% of all BCCs carry a mutation in PTCH 1 or SMO, two conducting proteins of the Hedgehog pathway (Hh). Therefore, inhibition of the Hh pathway is a promising option for systemic first-line therapy. Vismodegib was the first developed of these small molecules, which was approved by the FDA in January 2012. **AREAS COVERED:** The authors review current treatment modalities for BCC and discuss current developments in pharmacological therapy. The current literature including meta-analyses, the Cochrane database and registered as well as completed randomized controlled trials. **EXPERT OPINION:** Hh inhibitors are a new promising treatment option for patients with advanced or metastatic BCC. Phase I and II clinical trials with the Hh inhibitor, vismodegib, showed a significant reduction in tumour size and appearance of new tumours with relatively good tolerability. Nevertheless, further investigation on new molecules and the effectiveness of an intermittent dosing regimen is necessary.

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Basal cell carcinoma: A paradigm for targeted therapies

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Abstract

Introduction: Basal cell carcinoma (BCC) is the most frequent cancer with increasing incidence over the last decades. Standard of care is surgical excision, upon which complete tumor clearance achieved in most cases. However, a small subgroup of patients will have remanence of disease post-excision and require further treatment options.. Over 90% of all BCCs carry a mutation in PTCH 1 or SMO, two conducting proteins of the Hedgehog pathway (Hh). Therefore, inhibition of the hedgehog pathway is a promising option for systemic first-line therapy. Vismodegib was the first developed of these small molecules, which was approved by the FDA in January 2012. **Areas covered:** The authors review current treatment modalities for basal cell carcinoma and discuss current developments in pharmacological therapy. The current literature including meta-analyses, the Cochrane database and registered as well as completed randomized controlled trials on www.ClinicalTrials.gov.

Expert opinion: Hedgehog inhibitors are a new promising treatment option for patients with advanced or metastatic BCC. Phase I and II clinical trials withthe Hedgehog inhibitor, Vismodegib, showed a significant reduction in in tumor size and appearance of new tumors with relative good tolerability.. Nevertheless, further investigation on new molecules and the effectiveness of an intermitting dosing-regimen is necessary.

1. Epidemiology

Basal cell carcinoma (BCC) is the most frequently diagnosed skin cancer and most common cancer in humans of European ancestry with increasing rates of incidence ¹. It comprises approximately 70% of all cutaneous cancers in Europe. Reliable data of the precise incidence are rare due to unsystematic documentation of diagnoses. However, the cancer registry for West-Switzerland has clearly documented an ongoing increase in incidence in males from 70 / 100'000 per year in 1980's to 140 / 100'000 per year in 1990's with continuing trend. According to these data, estimated lifetime risk for BCC development in the collective of newborn children in Switzerland in the year 2000 is at least 1:10 ². BCC causes considerable morbidity and is one of the most expensive cancers to the health care managing systems ³.

2. Aetiological risk factors and Pathobiology

The overall lifetime risk for BCCs is estimated to be approximately 30%. The risk of development increases with age reaching its peak during 6th – 8th decades. The incidence is higher in males than in females. The history of at least one BCC bears a cumulative risk of more than 40% for developing further BCCs within the next 3 years. This suggests genetic alterations - besides pre-existence of other risk factors ⁴.

The most important exogenous risk factor is exposure to ultraviolet (UV) radiation. Genotoxic damages induced by UV-B radiation (290 – 315 nm wavelength) ⁵⁻⁷ is linked to the history of multiple sun burns in early ages and intensive intermittent sunlight exposure ^{8,9}. The incidence of BCC is non-linearly correlated to the total UV exposure with peak at approximately two fold at 10,000–35,000 hours total sun exposure and remaining stable rates with additional exposure ^{10, 11}.

Accordingly, lifestyle-related usage of indoor tanning and sun seeking behaviour might explain data showing increased incidence rates of BCC in younger population and women ¹². Further risk factors are frequent x-ray irradiation ^{13, 14} and arsenic exposure ¹⁵ with known mutagenic effects on genes such as p53. Additionally, the combination of arsenic and UV radiation enhances UV induced genotoxic damages by arsenic and its metabolite ¹⁶⁻¹⁹.

Iatrogenic immunosuppression - particularly in organ transplant recipients - is another risk factor for BCC development depending on duration and dosage of immunosuppressants ²⁰. In immunocompromised population either caused iatrogenic or diseases such as AIDS, lymphoma or leukaemia BCC occur more often, in multiple numbers, aggressive forms and unusual locations ²¹⁻²³.

One of the most important genetic risk factor is fair skinned type I-II ²⁴, which is based on the presence of melanin subtypes pheomelanin (red-yellow pigment) and eumelanin (brown-black pigment) that have protective role against UV radiation. In patients with albinism there the lack of melanin production due to mutation in the TYR gene, which results in increased photosensitivity and enhanced risk for developing BCCs, SCCs and melanoma ²⁵. In case of variations of the melanocortin 1 receptor gene (*MCL1*) that encodes the receptor for α -melanocyte-stimulating hormone (α MSH), which is responsible for the switch between eumelanin and pheomelanin and determining the intensity of skin pigmentation ²⁶, the risk for developing BCC is increased ^{27, 28}.

Mutations of tumour suppressor genes such as p53 and patched homologue 1 (PTCH1) are observed in more than 90% of BCCs and have been proven to be essential for its pathogenesis ²⁸⁻³⁰. BCCs are common early in life in patients with hereditary syndromes such as the Gorlin-Goltz-syndrome ³¹, Xeroderma pigmentosum ^{32, 33 24}, Rombo-syndrome ³⁴ or Bazex-Dupré-Christol-syndrome ³⁵. Patients who are affected by those syndromes, present BCCs already in early childhood ³⁶⁻³⁸. Sunscreens use by patients with history of BCC, showed that

the number of p53 mutations in tumours decreases upon UV protection underscoring the importance of consequent UV protection, especially in these patients ³⁹.

Most of basal cell carcinomas occur sporadically. Hereditary autosomal dominant Basal-cell nevus syndrome (Gorlin-Goltz syndrome or nevoid basal-cell carcinoma syndrome) is characterized by prominent susceptibility to develop multiple (up to hundreds) BCCs ⁴⁰ and higher risk to develop other malignancies, especially medulloblastomas. Results of molecular genetic analysis revealed mutations in patched homologue 1 (*PTCH1*) gene located on chromosome 9q22 ⁴¹⁻⁴⁴. PTCH1 inhibits hedgehog (Hh) signalling pathway. Inactivating mutations in PTCH1 lead through loss of inhibition to pathway up-regulation and development of BCC ^{45, 46}.

2.1. Hedgehog Pathway

Hedgehog (Hh) signalling pathway is a driving force of carcinogenesis with mutations found in more than 70% of sporadic BCC ^{47, 48}, and 20-30% of medulloblastoma ^{49, 50}.

The Hh pathway was initially discovered in *Drosophila melanogaster* ⁵¹. This pathway is important for the embryonic development and differentiation of the cells.

In adults, the Hh pathway is turned off in normal cells, except the cells hair, skin and stem cells ⁵².

Hh signalling pathway entitled after the family of extracellular Hh ligands, includes several molecules that have ability mutually control their activity. The Hh family of protein ligands consists of three members: Sonic Hedgehog (SHh), Desert Hedgehog (DHh) and Indian Hedgehog (IHh) with capability to bind to PTCH (Figure 1). PTCH1, a 12-pass transmembrane receptor protein, has inhibitory action by binding to G protein-coupled receptor-like protein Smoothened (Smo), which serves as an pathway activator. Investigation in medulloblastoma demonstrated that in the absence of SHh ligand, PTCH inhibits Smo

from being activated into SmoC, which leads to activation of transcription factor GLI 1/2/3 through a series of protein interactions. Gli 1/2/3 regulate many genes that are active in stem cells.

Khavari et al. reviewed experimental mouse models and clearly indicated that basal cell carcinoma in contrast to squamous cell carcinoma of the skin and cutaneous melanoma undergoes far less genetic alterations. Certainly it is important to target multiple pathways if they are clear drivers of the malignancies.

SHh-overexpressing cells lead to expression of BMP-2B and bcl-2 - both Hh targets. Regenerated in immunodeficient mice, the histologic features of BCCs were shaped in the skin as well as the gene expression abnormalities of BCCs as decreased BP180/BPAG2 and laminin 5 adhesion proteins as well as expression of basal epidermal keratins were found^{53, 54}

Besides PTCH, suppressor of fused (SUFU) was verified as negative regulator of Hh pathway by inhibiting Gli1 and Gli2 from entering the nucleus and converting Gli into its repressor form (GliR) with consecutive function as transcriptional repressor on the Gli target genes.

In contrast, activated Gli (GliA) is associated with changes in transcription which leads to cell proliferation and differentiation^{55, 56}. In addition, Smo accumulation relieves the suppression exerted by SUFU on the Gli transcription factors. Accordingly, inactivation of inhibitors PTCH1 or SUFU, caused by either mutation or otherwise degradation, as well as activation of Smo lead to Hh pathway activation⁵⁷.

3. Clinical and histological aspects of BCCs

The cell of origin in BCCs with its importance for pathogenesis and further development of targeted therapies is still not identified. Xenograft models showed that BCCs arise from keratinocytes in the epidermis. However, in these publications demonstrated assumptions differ between its origin in hair follicular bulge stem cells or long-term resident progenitor

cells of the interfollicular epidermis and upper infundibulum, in basal cell compartments of the epidermis, growing hair follicle or sebaceous glands depending on model and conceivably on histological subtype of BCC⁵⁸⁻⁶¹.

BCCs are a heterogeneous group of tumors with varying clinical presentations and histological morphologies.

Nodular BCC (nBCC) is the most common BCC, occurring most frequently on sun exposed areas in head and neck region and typically presents as an elevated reddish nodule with a shiny, translucent, tensed surface and teleangiectasias. The typical pearl-chain-like appearance at the edges, ulceration, cystic differentiation or pigmentation may also be found. The histopathological evaluation reveals basophilic lobules, columns or cords with peripheral palisading and cleft formation between tumor nests and the stroma as well as trichogen differentiation or sebaceous features.

Superficial BCC (sBCC) presents clinically as erythematous patch with sharp demarcation and signs for erosions occurring in all body areas, especially in notsun-exposed areas such as the trunk. Their size may vary between a few millimeters up to many centimetres in diameter. Superficial lobules of basaloid cells confined to the papillary dermis, subepidermal tumor cell nests, accompanied by a pronounced stroma reaction with few inflammatory cells are seen on histopathology. Mixed patterns with nodular or an infiltrative component are rare but may occur.

Morpheic BCC presents as an infiltrated plaque, - flat or even sunken – lesion with poorly defined margins. Histologically, strands and nests of tumor cells are diffusely infiltrating, sometimes perineurally infiltrated and associated with a dense fibrous stroma reaction. Margins are often clinically underestimated.

Less frequent subtypes are micronodular BCC, trichogen differentiated BCC, fibroepithelial BCC (Pinkus tumor) or Basosquamous carcinoma.

Metastasis

BCC with metastases are rare and controversially discussed. Recent retrospective analyses of the medical literature identified 172 cases published between 1981 and 2011. The median survival after the diagnosis was 54 months. As expected, the survival time is shorter for distant metastases (24 months) compared to local regional metastasizing BCCs (87 months).

4. Current therapy of BCC

4.1. Surgery, radiation, cryosurgery, photodynamic therapy

Surgical excision with intra- or postoperative examination of the excised tissue to histologically confirm the clinical diagnosis is the gold standard of therapy.

Only a small percentage of BCCs are unresectable or excision could lead to unacceptable functional and cosmetic defects. The unresectable BCCs are considered to be locally advanced and may even be associated with metastases. Repeated surgical excisions can be problematic especially for those with genetic disorders and the predilection for multiple BCCs during their lifetime such as seen in Gorlin-Goltz-syndrome. Prior to the development of new targeted therapy, treatment options for locally advanced BCCs and metastatic BCCs were very poor.

The decision between conventional surgery with predetermined safety margins or a stepwise excision with correlated microscopical examination of peripheral and deep surgical tissue margins dependson patient's risk factors such as tumor size and site, definition of clinical

margins, histological subtype and features of aggression, failure of previous treatment and immunosuppression.

In primary BCCs, conventional surgery with a safety margin according to subtype and size of the tumor is highly effective. The recommended safety margin is 3-5mm in small, well defined lesions and wider excisions are recommended in morphoeic and larger BCCs.

Micrographic approach by Mohs or slow-Mohs (histographically controlled tumor margins on paraffin sections) surgery are indicated for aggressive subtypes such as morphoeic, basosquamous, micronodular or infiltrative BCCs, recurrent or extended (>2cm) tumors as well as difficult facial localizations with little skin reserves, perineural or perivascular involvement and poor clinical definitions of tumor margin ⁶²⁻⁶⁵.

In case of multiple BCCs -or when surgery is impractical- other alternatives can be considered. Cryotherapy can be taken into account in presence of low risk solitary or multiple BCC with small and superficial lesions, especially in older patients or periocular localization. Disadvantages might be lower cure rate and sub-optimal cosmetic results caused by hypopigmented scars compared to surgical excisions ⁶⁶.

Moreover, Photodynamic therapy (PDT) is recommended for the treatment of sBCC and nBCC with a tumor thickness of 2 mm. This technique requires the simultaneous presence of a photosensitizer such as topical Aminolevulinic acid (ALA) or Methyl- ester derivate (MAL) - which can enhance penetration and have a higher tumor selectivity, – combined with an activating light and molecular oxygen ⁶⁷.

In a sBCC prospective randomized multicenter trial, photodynamic therapy (MAL-PDT) demonstrated a better cosmetic outcome with similar high efficacy compared to surgery ⁶⁸.

Radiotherapy using superficial x-rays or electrons is a suitable alternative especially in patients of advanced age (>60 years), anatomically critical localizations such as the periorbital region or when surgery is contraindicated.² Nevertheless, radiotherapy is not suitable for morpheic or desmoplastic BCC due to the high risk of recurrence⁶⁵.

4.2. Chemotherapy

5-Fluorouracil (5-FU)

5-FU is a pyrimidine analogue that inhibits the enzyme thymidylate synthase and thereby prevents DNA synthesis in tumor cells. In multiple superficial low risk, extrafacial BCCs or in patients with Basalcell naevus syndrome, topical 5-FU treatment can be contemplated. Limited indications for treatment with 5-FU are based on studies showing that despite clinical appearance of tumor control achieved by superficial inhibition of growth, deeper tumor parts are not treated sufficiently and might continue to expand. Additional to DNA synthesis inhibition, 5-FU shows effects and interaction on Hedgehog pathway. In vitro investigations in human hepatocellular carcinoma cell lines suggested that 5-FU can down-regulate target molecules of the Hh Pathway at both mRNA and protein levels. Concerning effectiveness of combination 5-FU with smo inhibitor, cyclopamine, mouse models in pancreatic tumours showed significantly higher tumour volume in mice injected with cyclopamine and 5-FU than in those injected with 5-FU alone. Concluded that Smo inhibitors may increase chemoresistance in some chemotherapy drugs like shown in hypoxic pancreatic cells⁶⁹.

4.3. Imiquimod

Application of topical imiquimod 5% is recommended in multiple sBCC, low risk BCCs and extrafacial localizations. Imiquimod is an imidazoquinolin causing inflammation with IFN- α driven immune response, inducing T cell mediated immunity and pro apoptotic effects. It directly activates innate immunity effectors such as plasmacytoid dendritic cells (PDCs) by

triggering toll-like receptor 7/MyD88/NF- κ B pathway, leading to induction, synthesis and release of various cytokines, in particular IFN. Correlation between expression levels of IFN- α -inducible genes and PDC counts, as well as tumor regression was shown⁷⁰. Additionally, imiquimod exerts pro-apoptotic activity against tumour cells with verified decrease of Bcl-2 expression⁷¹ and tumor suppressor function by induction of Notch signaling pathway whose activity is known to be decreased in BCCs by up-regulating protein expression of the Notch ligand, Jagged1 resulting together with its pro-inflammatory properties in tumor regression. Topical imiquimod 5% has been consistently superior to placebo in the treatment of immunocompetent patients with superficial BCCs in randomized, double-blinded trials. Complete clinical and histologically-verified clearance of the tumors occurred in 79–87% of imiquimod-treated patients after five-times-weekly or daily administration for 6-12 weeks. Similarly designed trials involving nodular BCCs were also performed, showing slightly lower histologically confirmed clearance of the treated tumors in 70-76% cases^{72, 73}. The 5 year follow up study showed clinical clearance rate of 89,6%, 12 weeks post-treatment and clinical clearance and histological clearance of 77.9% and 80.9%, respectively, at the end of follow-up after 5 years⁷⁴.

4.4. Targeted therapies on Hh Pathway

4.4.1. Cyclopamine

The first well studied targeted therapy of the Hh pathway, was cyclopamine, an endogenous steroidal plant alkaloid derived from corn lilies⁷⁵. Cyclopamine competitively inhibits Smo by binding directly to the transmembrane domain of the protein. This induces midline deformities in embryogenesis⁷⁶ and leads to growth inhibition in malignant cells^{75, 77}.

Already in 2004, there was a report on the topical use of this inhibitor in few BCC patients. All of them experienced clinical improvement with histological tumour regression attributed to induction of apoptosis⁷⁸. Consequently, synthetic Cyclopamine derivatives were developed to optimize the inhibitory effects on the Hh signaling and encouraged elaboration of small molecule antagonist of Smo were found (e.g. GDC-0449, LDE225). The most promising specific Hh inhibitor was Vismodegib (GDC-0449, Genentech), for which could be shown to have efficacy in patients with medulloblastoma⁵¹.

4.4.2. Vismodegib

Vismodegib (2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide) has shown *in vivo* activity in preclinical models of medulloblastoma⁷⁹, colon and pancreatic tumours^{80, 81}. In phase I clinical trials, vismodegib was relatively well tolerated with pharmacodynamic evidence of hedgehog pathway inhibition including GLI I suppression. A dose of 150 mg established a reasonable safety profile and stable serum levels (80). A bioavailability of 31.8% was shown after a single dose of 150mg vismodegib in a clinical trial with healthy young women (83). Vismogdegib has a hepatic clearance of 82% and renal clearance of 4% (84).

Von Hoff et al. reported a clinical trial investigating the safety and pharmacokinetics of vismodegib and tumor response in advanced BCCs with different dose levels. 18 of total 33 patients experienced an objective tumour response including two complete remissions. In general, the treatment was comparatively well tolerated. Most common side effects (grade 2-4) include fatigue, hyponatremia muscle spasm and weight loss. Increasing the dose did not result in higher blood plasma concentrations. The level of GLI down-regulation did not

correlate with the pharmacokinetic level of vismodegib in individual patients (81). Based on this data, a pivotal phase II clinical trial was initiated in patients with metastatic or locally advanced BCCs. The data presented by Sekulic et al. (82), have been updated and presented at the European Society of Medical Oncology Meeting in Vienna 2012. The investigators observed a 33.3 % response rate for metastatic BCCs and a 47.6% response rate for locally advanced BCCs (Table 1). The median duration of response was 7.6 months for metastatic BCCs and 9.5 month for locally advanced BCCs. Progression-free-survival was 9.5 months for both groups. Most frequent adverse effects included muscle spasm 71%, alopecia 65% and dysgeusia 53%, weight decrease 50% and fatigue 40% ⁸².

Currently, a global single arm open label safety study with vismodegib in patients with advanced BCC (STEVIE study) is ongoing. The second interim analysis of this study was presented at the EADV meeting in Prague, September 2012. At this time point, already 150 patients had a follow up of ≥ 3 months (138 patients with locally advanced and 12 with metastatic BCCs).. A preliminary best response was available for 124 patients. 19.4% experienced a complete response whether a partial responses were seen 55.6% of the patients ⁸³. Muscle spasms, alopecia, dysgeusia, asthenia and weight loss were the most common adverse effects.

In September 2012, 423 patients have been recruited in 15 countries including Switzerland. The recruitment is ongoing.

During the same time period, another phase II study with vismodegib was performed. I. Epstein and D. Bickers' research groups investigated patients with Gorlin-Goltz syndrome (85). 41 patients were included in this randomized, double-blind, placebo-controlled trial. They were randomized 2:1 to receive vismodegib 150mg per day or placebo. Vismodegib therapy induced regressions of pre-existing BCCs and prevented the development of new BCCs in this patient population. At the planned second interim analysis in December 2010,

the data safety and monitoring board recommended ending the placebo treatment owing to statistically significant differences in efficacy favoring the vismodegib group.

Vismodegib was approved under the trade name Erivedge[®] as the first Hedgehog pathway inhibitor, by the food and drug administration (FDA) in the US on January 30, 2012.

4.4.3. Itraconazol

The systemic antifungal drug itraconazol, an azol derivate that inhibits biosynthesis of ergosterol and cholesterol, was recently identified as an antagonist of Hh signaling. In vitro and mouse models demonstrated that itraconazol shows Smo- antagonism by binding as inverse agonist, leading to inhibition of Hh signaling pathway and tumor regression in medulloblastoma and BCC.

As a result, further azol antifungals from the imidazole and triazole type such as fluconazole were tested but had no effects on Hh signaling pathway. It was concluded that inhibition of the Hh pathway is not due to a general class effect of azole-derivates. Additionally, a lipid interfering effect in blocking Hh reception through presumed sequestration of itraconazol by LDL was detected ⁸⁴.

According to these data, an ongoing open-label exploratory phase II clinical trial of oral itraconazol for the treatment of basal cell carcinoma is currently performed. Recently published data on 19 patients treated with oral itraconazol 200 mg/d for 1 month or 400 mg/d for a not specified duration, showed a reduction of BCC tumor size with 23% reduction in clinical tumor area, 45 % reduction of tumor proliferation and 65% in Hedgehog pathway activity ⁶⁵.

Further and long term results for the clinical relevance in the treatment of BCCs longtime known antifungal will be needed.

4.4.4. LDE 225

LDE225, N-(6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)-2-methyl-4-(trifluoromethoxy)biphenyl-3-carboxamide, is a potent and selective small-molecule inhibitor of SMO, which is structurally distinct from cyclopamine.

LDE 225 was investigated in a dose escalation phase I clinical trial in patients with advanced solid tumors. Most patients included in this trial suffered from locally advanced or metastatic BCC or recurrent medulloblastoma. 103 patients were included, from which 73 received the drug once daily and 30 patients received it twice daily. Most common adverse effects included nausea dysgeusia, weight loss, muscle spasms and myalgia often associated with increase of the serum creatin kinase (CK levels). In addition, alopecia and dysgeusia have been observed. The dose limiting toxicity was grade 3 / 4 - serum CK elevation at a dosage of more than 800 mg once daily or > 250 mg twice daily. This dose limiting toxicities were observed 3 and 6 weeks after treatment initiating, respectively. 6 of 16 patients with BCC (37%) and in addition 3 of 9 patients with medulloblastoma (33%) achieved objective tumour responses. Based on these promising results (J. Rodon et al., paper submitted), a randomized double-blind phase II clinical trial was initiated comparing the efficacy and safety of two levels of LDE 225 in patients with locally advanced BCC and metastatic BCC⁸⁵. One experimental arm is dosing LDE 225 at a dosage of 200 mg daily; the other arm applies 800 mg daily. The primary objective is the rate of objective responses after 6 months of treatment.

Topical

LDE 225 was also investigated as topical treatment in a doubleblind randomized vehicle-controlled trial in 8 patients with Gorlin-Goltz syndrome. 27 BCCs were treated twice daily with a 0.75% LDE 225 cream or vehicle for 4 weeks. The topical therapy was well tolerated. There was hardly any inflammation. 3 out of 13 with LDE 225 treated BCCs showed a complete remission and 9 a partial remission clinically. However, histological investigations still showed remaining tumour nests that presented with reduced proliferation as assessed immunohistochemical by using expression of ki67 ⁸⁶.

4.4.5. LEQ 506 and other smoothened inhibitors

The efficacy and tolerance of further substances such as PI-926, BMS-838923 (XL139), TAK-441, PF-04449913 and LEQ, are currently explored in phase I and II trials for patients with BCCs as well as in patients with medulloblastoma or other cancerse.g. 506 ⁸⁵. The results of these studies are currently not available.

. An ongoing phase II study in pediatric patients from 3 to 21 year old patients with medulloblastoma are treated with vismodegib ⁸⁷. Data on geriatric patients are limited so far. So far no phase III trials have been initiated for Hh inhibitors due to the fact of missing compareable treamtents.

Highlight Box

- Basal cell carcinomas (BCC) are the most frequent cancer in human beings and standard of care is the surgical excision.
- Over 90% of all BCC have a mutation in PTCH 1 or SMO, two conducting proteins of the Hedgehog pathway.

- Hedgehog inhibitors are a new option for a systemic treatment for locally advanced or metastatic BCC.
- Vismodegib was the first drug to be approved by the FDA.
- The most side effects are mild and overall well tolerated.

5. Side effects

Von Hoff et al. reported no grade 5 adverse events and only one grade 4 event was seen (asymptomatic hyponatremia). Several grade 3 events have been reported: fatigue, hyponatremia, weight loss, dyspnea, muscle spasm, atrial fibrillation, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection and prolonged QT interval for vismodegib ⁸⁸.

1 out of 33 patients decided to discontinue the treatment after 8 months because of ongoing grade 1 adverse events (abdominal pain, fatigue, weight loss, dysgeusia) and grade 2 anorexia. In the study of Sekulic et al., all 104 patients had at least one adverse event ⁸⁹. 57% showed grade 1 and 2 events, which was consistent with those from the phase I study. Grade 3 and 4 adverse events included muscle spasms, weight loss, fatigue and loss of appetite (Table 2). 25% of the events were considered serious adverse events and 7 patients experienced grade 5 events (including death from unknown cause, hypovolemic shock, myocardial infarction, meningeal disease and ischemic stroke). The relationship of these fatal events and Vismodegib are unknown as they showed no definite pattern and all patients had clinically significant risk factors or coexisting conditions at baseline.

About half the patients had discontinued the study at a median treatment duration of approximately 10 months. 18% in the metastatic BCC group because of disease progression

and in the other cohort 25% of the patients decided to stop the treatment on their own with to us unknown reasons.

Tang et al. observed mild or moderate adverse events and no grade 5 events⁹⁰. Patients receiving Vismodegib had significantly more adverse events than patients on placebo.

Also in this study patients have withdrawn their consent due to adverse events. The ceased shortly after ending with vismodegib: dysgeusia and muscle cramps within 1 month and the regrowth of hair were observed within 3 months.

The adverse events of vismodegib are similar in all clinical trials done so far. The assumption is that they are mechanism-related.

Hair follicle growth is initiated by the WNT signaling that induces the formation of the dermal condensate⁹¹. For further development of the hair the Hedgehog pathway is required. Chiang et al. could show in their experiments with mice that hair germs consist of epidermal placodes and associated dermal condensates and are found in both, the control and the Shh -/- embryos. For the progression in the further development of the hair follicle the Sonic Hedgehog is needed and therefore this process is blocked in mutant skin⁹².

Furthermore, these rudimental hair follicles are capable of a localized growth and differentiation, but unable to form a normal hair⁹³.

Similar to the process in the development of the hair, the Hh pathway also required for growth and patterning of the lingual taste papillae. Investigations on mice performed by Hall et al. as well as Liu et al. demonstrated that disruption of the Hh signaling pathway during embryogenesis results in an irreversibly altered number and location of fungiform papillae on the anterior tongue. Once papillae are well formed, hedgehog pathway is needed for the maintenance of the interpapillae space and papillae-free regions on the tongue^{94 95}.

6. Resistance

Despite the promising results vismodegib showed in the past few years, there is already evidence about resistance to vismodegib. Rudin et al. reported in 2009 the case of a 26-year-old male patient with medulloblastoma, who developed resistance after 3 months of therapy despite response at the beginning. The reason for the resistance was a heterozygous G to C missense mutation in SMO at position 1697 and changed the codon 473 from Asp to His (D473H). That led to an ineffective binding of vismodegib^{51 96}.

Further research on the mechanism of resistance was performed by Dijkgraaf et al. They could proof that a modified SMO with an exchange of the amino acid aspartic acid at position 473 resulted in a less sensitive binding of vismodegib than wild-type SMO⁹⁷. In addition they determined that mutation in E518 of SMO leads to a complete resistance of SMO to vismodegib. The amplification of GLI2 downstream of SMO was another mechanism of resistance to vismodegib⁹⁷.

Itraconazol, a systemic azole antifungal agent, was recently detected to inhibit SMO in the Hh signaling pathway, but with another mechanism than the one of cyclopamine and with a less significantly potency than the currently available Hh inhibitors⁸⁴. According to the resistance by amplification of GLI2 it is also supposable to block the GLI function to overcome resistance. One such substance in development is GANT61⁹⁸. The identification of second-generation SMO antagonists that show efficacy in SMO-Wildtype as well as SMO-mutants may be another suitable way to overcome resistance⁹⁷.

Another potential resistance mechanism is the up-regulation of the phosphoinositide 3-kinase (PI3K) pathway. It was detected that in NVP-LDE225-resistant samples (a new potent and selective oral SMO inhibitor from a newly described structural class⁹⁹. IGF1R-PI3K target genes were much upregulated comparing to drug-sensitive samples¹⁰⁰. This implicates that

the PI3K pathway is involved in the resistance mechanism of the Hh pathway. Targeting the PI3K pathway may provide a suitable solution in the situation of Hh

resistance. First encouraging results have been shown by Engelman et al.¹⁰¹.

So far there are no proven salvage therapies available to overcome acquired Hedgehog resistance, but the above mentioned ways are all promising approaches to therapy and need further investigation.

7. Conclusion

A careful analysis of the molecular pathways has identified the Hedgehog signaling pathway to be a key player involved in the biology of basal cell carcinoma and other cancer cells. This pathway is active during embryogenesis and essential for the orientation of the nervous system and other important compounds of a multi-organ organism. In adults this pathway is physiologically turned off, except in the stem cells of hair follicles, where it is essential for the re-initiation of the hair cycle. Because the activation of this pathway is limited especially to hair follicle cells and to basal carcinoma cells, it is a valuable targetable pathway in cancer therapy, providing a new promising treatment option for patients with advanced BCC and metastatic BCC as well as other tumors depending on the hedgehog pathway including medulloblastoma. Consequently, smoothened(SMO) inhibitors have been developed by several companies and successfully introduced into the clinics Vismodegib was very recently registered by the FDA (USA) for the treatment of advanced or metastatic basal cell carcinoma. Other substances will follow in the near future.

In general, these molecules are well tolerated by the patients. However, the results of a long term use showed considerable discomfort of quality of life caused by the sum of all the side effects (muscle pain, dysgeusia and probably related to dysgeusia weight loss). This peculiar

spectrum of adverse effects can be challenging to manage especially in the typical BCC patient population of advanced age and many co-morbidities. The clinical research community has to develop strategies to cope with these problems. Intermittent dosing might be one of the options besides the search for supportive measures.

The clinical data, which are available today, show convincingly the potency of smoothened inhibitors. However, they have never been investigated in randomized clinical trials. It might make sense to compare them to chemotherapy in very advanced basal cell carcinomas and explore topical strategies in patients with multiple basal cell carcinomas, including patients with Gorlin-Goltz syndrome.

Based on the recently reported promising response rates, smoothened inhibitors might also be valuable drugs for the neo-adjuvant use in conjunction with surgery. In addition they might increase the radio sensitivity of basal cell carcinomas. These clinical questions have to be addressed in clinical trials in the near future.

Furthermore, the studies in patients with Gorlin-Goltz syndrome indicate, that the systemic treatment with smoothened inhibitors can also prevent the development of new basal cell carcinomas in a high-risk patient population. Based on the fact that there is a substantial number of patients, who continuously develop new basal cell carcinomas, smoothened inhibitors hold promise for the chemoprevention of this very common skin carcinoma.

In patients with a low tumor burden, the topical use of smoothened inhibitors should be explored in more detail. Early results have indicated some efficacy for this treatment, however there is no information on the histological clearing of the tumor cells and the optimal time and

dosing of topically used smoothened inhibitors. This approach would definitely avoid the significant side effects, especially after long term treatment of this drug class.

In our opinion, smoothened inhibitors are essential in the repertoire of small molecules inhibitors. The importance of the Hedgehog signaling pathway in other malignancies is under investigation.

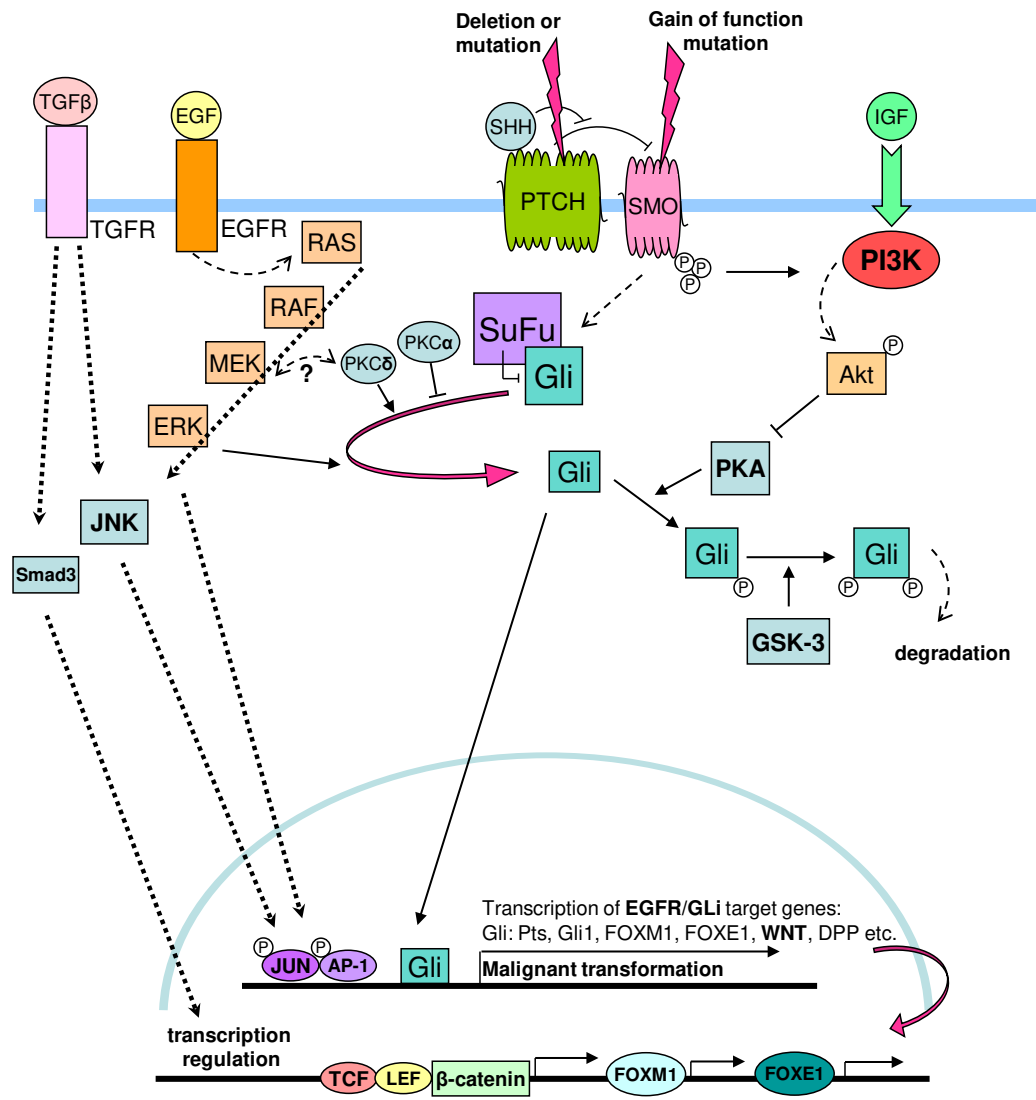


Figure 1: Hedgehog pathway in basal cell carcinoma cells.

	mBCC (n=33)		laBCC (n=63)	
	26 November 2010	28 November 2011	26 November 2010	28 November 2011
OR, n (%) (95% CI)	10 (30.3) (15.6 - 48.2)	11 (33.3) (19.2-51.8)	27 (42.9) (30.5-56.0)	30 (47.6) (35.5- 60.6)
Complete response, n	0	0	13	14
Partial response, n	10	11	14	16
Stable disease, n	21	20	24	22
Progressive disease, n	1	1	8	8
Missing or NEv	1	1	4	3
Median DOR, months (95%CI)	7.6 (5.6- NE)	7.6 (5.5- 9.4)	7.6 (5.7- 9.7)	9.5 (7.4- 21.4)
Median PFS, months (95%CI)	9.5 (7.4- NE)	9.5 (7.4- 11.1)	9.5 (7.4- 11.9)	9.5 (7.4- 14.8)
BCC= basal cell carcinoma; CI= confidence interval; DOR= duration of response; laBCC= locally advanced BCC; mBCC= metastatic BCC; NA= not available; NE= not estimated; NEv= not evaluable; ORR= objective response rate; PFS progression- free survival				

Table 1: Updated response rates by independent reviewers of the ERIVANCE BCC study for patients under treatment with vismodegib 150mg per day. For patients with locally advanced

BCC an overall response rate of 47.6% was seen. For metastatic basal cell carcinoma the ORR was 33.3%⁸².

Event	Any Grade	Grade 1	Grade 2	Grade 3 or 4
<i>In percentage of patients</i>				
Muscle spasms	68	48	16	4
Alopecia	63	49	14	0
Dysgeusia	51	28	23	0
Decrease in weight	46	27	14	5
Fatigue	36	27	5	4
Nausea	29	21	7	1
Decrease in appetite	23	14	6	3
Diarrhea	22	16	5	1

Table 2: Reported adverse events in the Erivance BCC study under treatment with vismodegib 150mg per day⁸⁹.

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